Kindly add the following new claims:

21. (NEW) A method for substantially simultaneously visualizing epithelial origin of a cell and the chromosome count of the cell comprising, in the following order:
a. obtaining a biological sample containing a cell from a patient;
b. performing immunocytochemistry on the sample to indicate epithelial origin;
c. analyzing the stained cell for chromosomal count.

B6

22. (NEW) The method of claim 21 wherein performing immunochemistry on the sample to indicate epithelial origin is treating the sample with a labeled antibody against cytokeratin.

23. (NEW) The method of claim 21 wherein analyzing the stained cell for chromosomal count is performing FISH analysis on the sample.

24. (NEW) The method of claim 1 wherein the biological sample is blood.

25. (NEW) The method of claim 1 whereby the hybridization pattern distinguishes a non-cancer cell from a cancer cell by detection of chromosomal aneuploidy specific for cancer.

REMARKS

Claims 1-20 are pending in this application. Claims 1, 7, 15, 17, and 19 have been amended. Claims 3-6 have been cancelled. Claims 21-25 have been added.

No new matter is believed to have been added to the amended or new claims.

OBJECTIONS

The examiner stated that the numbering of the claims was not in accordance with 37 C.F.R. 1.1.26 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are cancelled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (when entered or not).

The examiner stated that misnumbered claims 20 and 21 have been renumbered 19 and 20.

The claims as shown in the attached marked-up version also reflect this numbering correction.

35 U.S.C. §112, 1st ¶

Claims 15-20 were rejected under 35 U.S.C. 112, 1st paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement

Enablement requires that the specification describe how to make and use the invention. The invention that must be enabled is defined by the claim(s). MPEP 2164. Enablement is viewed from the perspective of the time at which the application was filed. MPEP 2164.05(a).

Before any analysis of enablement can occur, it is **necessary** for the examiner to **construe the claims**. For terms that are not well-known in the art or could have more than one meaning, it is **necessary** that the examiner **select the definition** that she/he intends to use when

examining the application and **explicitly set forth** the meaning of the term and scope of the claim when writing an Office action. In order to make a rejection, the **examiner** has the **initial burden** to establish a **reasonable basis to question** the enablement provided. A specification disclosure which contains a teaching of the manner and process of making and using in terms which correspond in scope to that of the subject matter sought to be patented **must** be taken as being in **compliance unless there is a reason to doubt the objective truth of the statements** contained therein. It is incumbent on the PTO, whenever a rejection for enablement is made, to **explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the statement**. The minimal requirement is for the examiner to give reasons for the uncertainty of the enablement. This standard is applicable even when there is not evidence in the record of operability without undue experimentation beyond the disclosed embodiments. MPEP 2164.04

The **standard** for determining whether enablement is met is "is the experimentation needed to practice the invention undue or unreasonable?" The disclosure in the patent is coupled with the information known in the art. Determination of enablement is a question of law based on underlying factual findings. The fact that experimentation may be complex does not necessarily make it undue. MPEP 2164.01.

The **factors** for determining satisfaction of the requirement include, but are not limited to:

(1) the breadth of the claims;

(2) the nature of the invention;

(3) the state of the prior art;

(4) the level of one of ordinary skill;

(5) the level of predictability in the art;

(6) the amount of direction provided by the inventor;

(7) the existence of working examples; and

(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosures. In re Wands.

Any conclusion as to non-enablement must be based on the evidence as a **whole**. MPEP 2164.01(a).

As long as the specification **discloses at least one method for making and using** the claimed invention that bears a **reasonable correlation** to the entire scope of the claim, then the enablement requirement is satisfied. MPEP 2164.01(b).

If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, the requirement is met. If multiple uses are disclosed, a rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use, *i.e.*, **if any use in enabled**, the application is enabling for the claimed invention. MPEP 2164.01(c).

Compliance with the enablement requirement does not turn on whether an example is disclosed. An applicant need not have actually reduced the invention to practice prior to filing. For a claimed genus, **representative example(s) together with a statement applicable to the genus** as a whole will ordinarily be sufficient. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that one of skill in the art could not use the genus as a whole without undue experimentation. MPEP 2164.02.

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. However, even in unpredictable arts, a disclosure of every operable species is not required. MPEP 2164.03.

Claim 15, Step d and Claim 16, Step e

The examiner states that claim 15 step d and claim 16 step e involve "determining the amount of cancer cells in the sample" and "correlating the amount of cancer cells in the sample with the stage of cancer." The examiner alleges that the specification does not teach what kinds of samples to use, what kind of cancer cells to look for, and what amount of cells is characteristic of a stage of cancer. There are many forms of cancer with many different forms of progression, and a large quantity of experimentation is required to correlate any marker with the stages of some particular form of cancer. In the absence of any guidance, it is concluded that undue experimentation would be required to practice this invention as claimed.

It is noted, and explained below, that the examiner has not used the correct standard nor met the burden of proof required of the examiner. To expedite prosecution, Applicants have explained why the claims are enabled to rebut the rejection in addition to why the rejection does not meet the legal standard required for a *prima facie* case. It is noted the Applicants need not rebut a rejection until the examiner has made a *prima facie* case.

The present specification is replete with direction and guidance on how to practice the invention with no more than routine experimentation.

"[D]etermining the amount of cancer cells in the sample" refers to the biological sample containing a cell from a patient diagnosed with cancer obtained from step a of claim 15 or claim 16. The "biological sample," is clearly described in the specification, for example, on page 15,

lines 12 to p. 16, line 21 and p. 30, lines 16-18 of the present application, the sample can be many different things, such as fluid (e.g., peripheral blood, sputum) or tissue (e.g., bone marrow, tissue sections, tumor). Further, the Examples also use blood specimens as the sample, e.g., p.28, lines 25-26, and p. 30, lines 6-8, 13-18. As for "determining the amount" of cancer cells in the sample, the specification discloses the following qualitative and/or quantitative methods for determining "amount," e.g., the cells are probed with cancer-cell specific nucleic acid probes and FISH analysis performed (p. 8, lines 17-18, 23-28); p. 10, lines 20-22; p. 16, line 28- p. 17, line 15; p. 18, lines 12-29 to p. 19, line 13; p. 21, lines 5-11; and p. 22, lines 13-26, especially, lines 20-21; the application provides examples of a multitude of detectable moieties and methods to quantify an amount based on them. As for which cells are "cancer cells" and what kind of cancer cells to look for, the specification provides the following information, e.g., p. 5, line 28 to p. 6, line 17; p. 9, lines 13-15, 20-21; p. 10, lines 13-15; p. 11, lines 6-9; p. 15, lines 9-10; p. 16, lines 23-28; p. 17, lines 17-29 to p. 18, line 29; p. 26, line 28 to p. 28, line 13; p. 29, lines 22-27; p. 30, lines 1-4; and p. 35, line 26 to p. 36, line 7. Examples of cancer include those affecting epithelial cells. Examples of cancer include prostate, breast, cervical, lung, pancreatic, brain, ovarian, liver, throat, esophageal, kidney, colon, or any other type of cancer (p. 11, lines 6-9). Examples of cancer cells are those cells that exhibit chromosomal aneuploidy specific for cancer (p. 6, line 3). Examples of tumor-specific antigens that can be used to enrich samples for cells associated with tumorigenesis include prostate specific antigen (PSA), CA125, Cyfra 21-1, and TPS (p. 7, lines 22-25). This all gives guidance as to types of cancer cells that can be targeted.

All of this information coupled with the knowledge in the art provides enabling disclosure for the claims.

"[C]orrelating the amount of cancer cells in the sample with the stage of cancer" refers to methods described, e.g., p. 10, lines 22-26; p. 12, line 27 to p. 13, line 6; and p. 15, lines 4-8.

All of this information coupled with the knowledge in the art provides enabling disclosure for the claims. One of skill in the art is clearly able to determine how correlations are determined, e.g., gathering two sets of data and determining the relationship between the two in systematic, routine experimentation.

The invention as defined by these claims is clearly enabled (teach one of skill in the art how to make and use). Applicants note that the subject matter of the claims is to be analyzed as a whole, not by its parts individually. MPEP 2164.08. Applicants note that the examiner has referred to specific steps within specific claims rather than claims as a whole. Further, the examiner must look to the specification to determine whether the claim is enabled, not whether the claim standing by itself without the specification is enabled. The examiner has clearly not met the initial examiner's burden by providing evidence as to why the truth of the statements made in the specification (such as those called out by page and line number above) are doubted (see above). Guidance has been provided and the examiner may not merely conclude undue experimentation would be necessary without providing evidence as to why undue experimentation is asserted to be required.

If the examiner believes there is a scope issue with enablement rather than an issue of any enablement, the examiner should point out limitations that the examiner believes would render the claims enabled (MPEP 2164.04, 2164.08), in addition to evidence supporting that conclusion.

Claim 17 and 18, Steps d, e

The examiner states that claims 17 and 18 (steps d and e) involve "determining the amount of cancer cells in the sample" and "correlated with progression of cancer." The examiner alleges that the specification does not teach what kinds of sample to use, what kind of cancer cells to look for, and what amount of cells is characteristic of progression of cancer.

There are many forms of cancer with many different forms of progression, and a large quantity of experimentation is required to correlate any marker with the stages of some particular form of cancer. In the absence of any guidance, it is concluded that undue experimentation would be required to practice this invention as claimed.

It is noted, and explained above, that the examiner has not used the correct standard nor met the burden of proof required of the examiner. To expedite prosecution, Applicants have explained above why the claims are enabled to rebut the rejection in addition to why the rejection does not meet the legal standard required for a *prima facie* case. It is noted the Applicants need not rebut a rejection until the examiner has made a *prima facie* case.

The present specification is replete with direction and guidance on how to practice the invention with no more than routine experimentation.

Examples of the locations within the specification that provide guidance and direction to one of ordinary skill related to the limitations are listed above.

All of this information coupled with the knowledge in the art provides enabling disclosure for the claims.

The invention as defined by these claims is clearly enabled (teach one of skill in the art how to make and use). Applicants note that the subject matter of the claims is to be analyzed as a whole, not by its parts individually. MPEP 2164.08. Applicants note that the examiner has referred to specific steps within specific claims rather than claims as a whole. Further, the examiner must look to the specification to determine whether the claim is enabled, not whether the claim standing by itself without the specification is enabled. The examiner has clearly not met the initial examiner's burden by providing evidence as to why the truth of the statements made in the specification (such as those called out by page and line number above) are doubted (see above). Guidance has been provided and the examiner may not merely conclude undue

experimentation would be necessary without providing evidence as to why undue experimentation is asserted to be required.

If the examiner believes there is a scope issue with enablement rather than an issue of any enablement, the examiner should point out limitations that the examiner believes would render the claims enabled (MPEP 2164.04, 2164.08), in addition to evidence supporting that conclusion.

Claim 19 and 20, Step d

The examiner states that claims 19 and 20 step d involve "determining the amount of cancer cells in the sample" and "correlating the amount of cancer cells in the sample with the effectiveness of the anti-cancer treatment." The examiner alleges that the specification does not teach what kinds of sample to use, what kind of cancer cells to look for, and what amount of cells is characteristic of the effectiveness of the anti-cancer treatment. There are many forms of cancer with many different degrees of response to a cancer treatment, and a large quantity of experimentation is required to correlate any marker with the treatment response of some particular form of cancer. In the absence of any guidance, it is concluded that undue experimentation would be required to practice this invention as claimed.

It is noted, and explained above, that the examiner has not used the correct standard nor met the burden of proof required of the examiner. To expedite prosecution, Applicants have explained above why the claims are enabled to rebut the rejection in addition to why the rejection does not meet the legal standard required for a *prima facie* case. It is noted the Applicants need not rebut a rejection until the examiner has made a *prima facie* case.

The present specification is replete with direction and guidance on how to practice the invention with no more than routine experimentation.

Examples of the locations within the specification that provide guidance and direction to one of ordinary skill related to the limitations are listed above. Further, as to effectiveness of treatment, guidance within the specification includes, e.g., p. 13, lines 6-7; p. 14, lines 18-29; p. 15, lines 1-10.

All of this information coupled with the knowledge in the art provides enabling disclosure for the claims.

The invention as defined by these claims is clearly enabled (teach one of skill in the art how to make and use). Applicants note that the subject matter of the claims is to be analyzed as a whole, not by its parts individually. MPEP 2164.08. Applicants note that the examiner has referred to specific steps within specific claims rather than claims as a whole. Further, the examiner must look to the specification to determine whether the claim is enabled, not whether the claim standing by itself without the specification is enabled. The examiner has clearly not met the initial examiner's burden by providing evidence as to why the truth of the statements made in the specification (such as those called out by page and line number above) are doubted (see above). Guidance has been provided and the examiner may not merely conclude undue experimentation would be necessary without providing evidence as to why undue experimentation is asserted to be required.

If the examiner believes there is a scope issue with enablement rather than an issue of any enablement, the examiner should point out limitations that the examiner believes would render the claims enabled (MPEP 2164.04, 2164.08), in addition to evidence supporting that conclusion.

For the above reasons, Applicants respectfully request that these rejections be withdrawn.

The examiner stated that for the prior art search purpose of the office, the examiner assumed the phrase "obtaining a biological sample containing a cell from a patient diagnosed with cancer" in the claims 15-20 means that the samples are from blood (see the first paragraph

of the specification) or other bodily fluid. However, this treatment does not relieve applicants of the burden of response to this rejection.

Applicants note that, for example, on page 15, lines 12-17, and p. 16, lines 11-12 of the present application, the sample can be many different things, such as fluid (e.g., peripheral blood, sputum) or tissue (e.g., bone marrow, tissue sections, tumor).

35 U.S.C. §102

WO 97/38313

Claims 1-15, 17 and 19 were rejected under 35 U.S.C. §102(b) as being anticipated by WO 97/38313 (IDS A2). The examiner asserts that claims 1-14 are drawn to cancer detection method by enriching circulating epithelial cells and detecting a hybridization pattern with a probe or multiple probes using various conventional detection methods.

The examiner states that WO 97/38313 teaches: 1) how to enrich cancer cells from various bodily fluid sources including blood (page 3, lines 1-17, page 6, line 3 to page 18, line 28); 2) how to enrich cancer cells of epithelial origin from blood (abstract and 2nd paragraph of page 1, first paragraph of page) by immunomagnetic beads (the 2nd paragraph of page 2), cytokeratin screening, and other methods (page 19, lines 15-17, page 20, lines 22-29); 3) detecting the hybridization pattern using various conventional detection methods (see page 21 to the first paragraph of page 26) and multiple probes (Example 7). The disclosed examples of probe associated with specific cancer and genetic marker are PSMA, PSA, and centromeric regions of chromosomes 7, 8, 18 (page 21-22). Further, the examiner states that WO 97/38313 teaches methods of determining status and progress of cancer patient, and monitoring efficacy of cancer treatment at page 3, lines 18-26, page 25, lines 19-26, examples 2, 7, and 11.

Applicants respectfully traverse the rejection.

WO 97/38313 discloses a method for enriching rare non-blood cells in a fluid sample comprising rare non-blood cells and non-rare cells, wherein the ratio of the rare non-blood cells to the non-rare cells is at least about 1:100,000, comprising obtaining a fluid sample, subjecting the fluid sample to density gradient separation and producing a first fluid comprising an increased concentration of rare non-blood cells and a second fluid comprising an increased concentration of rare non-blood cells, subjecting at least one of the fluids to a binding agent that binds non-rare cells, and removing the bound non-rare cells from the fluid(s) to provide fluid(s) enriched with rare non-blood cells.

The method of the WO 97/38313 first runs a fluid sample (1) through density gradient separation. This gives a sample (2) with an increased concentration of rare non-blood cells (cancer cells/epithelial cancer cells). Sample (2) is then subjected to a "negative selection process". This entails subjecting sample (2) to an agent that binds the non-rare cells (blood cells) rather than the rare cells (cancer cells) ("positive selection process") ("precisely the opposite of conventional processes," p. 7, line 31). The bound non-rare cells are then separated from sample (2). Then the rare cells can be further processed, such as by identification, characterization and/or culturing. Embodiments of the methods are asserted to provide improved diagnosis, staging, and monitoring of cancer in a patient.

The methods of the present invention are positive detection/selection processes. The enrichment is via binding of the cancer cell rather than the non-rare blood cells.

Claim 1 step a is "obtaining a cell from biological sample comprising a cell from a subject, wherein the sample is enriched for circulating epithelial cells by an agent binding with the epithelial cells." This step includes a "positive" selection enrichment (binding with the epithelial cells), therefore, WO 97/38313 cannot anticipate claim 1.

Claims 2-13 depend from claim 1, thus, these claims also cannot be anticipated.

Claim 14 includes step b: "mixing the biological sample with magnetic particles coupled to a ligand which is capable of reacting specifically with epithelial cells to the substantial exclusion of non-epithelial cells." Claim 14 is also clearly using a "positive" rather than "negative" enrichment method. The ligand reacts with the target epithelial cells rather than the non-epithelial cells in step b. This is clearly the opposite of what WO 97/38313 discloses. Therefore, step b is clearly missing from WO 97/38313 and, thus, WO 97/38313 cannot anticipate.

Claim 15 includes step b: "enriching the sample for circulating epithelial cells by an agent binding with the epithelial cells." This step includes a positive selection enrichment, therefore, WO 97/38313 cannot anticipate claim 15.

Claim 17 includes step b: "enriching the first and second samples for circulating epithelial cells by an agent binding with the epithelial cells." This step includes a positive selection enrichment, therefore, WO 97/38313 cannot anticipate claim 17.

Claim 19 includes step b: "enriching the sample for circulating epithelial cells by an agent binding with the epithelial cells." This step includes a positive selection enrichment, therefore, WO 97/38313 cannot anticipate claim 19.

These rejections should now be overcome.

Racila *et al.* (April 1998)

Claims 16, 18, and 20 were rejected under 35 U.S.C. §102(a) as being anticipated by Racilla [sic] *et al.* (IDS A26).

The examiner asserts that Racilla [sic] teaches cytometric and immunocytochemical methods (see the Methods section) using various antibodies that forms detectable complexes, that give a good correlation between changes in the level of tumor cells in the blood with status

and prognosis of a cancer, and the effectiveness of an anti-cancer treatment (abstract, Table 1, and Fig. 4).

Applicants respectfully traverse the rejection.

Racila is discussed in the present application on p. 28, line 29-p. 29, line 13. As pointed out on p. 29, lines 10-13 (emphasis added), "[t]his procedure has the capacity to detect whether epithelial cells are present in a sample, such as blood, but does not indicate the genetic status of the cells detected. Therefore further assays on the same sample are required to determine more conclusively the genetic status of these epithelial cells." The circulating epithelial cells were simply assumed to be tumor cells. (Applicants note that Jonathan Uhr is an author and contributor of the Racila *et al.* paper as well as an inventor of the present invention.)

Racila *et al.* (April 1998) disclose an assay combining immunomagnetic enrichment with multiparameter flow cytometric and immunocytochemical analysis to detect, enumerate, and characterize carcinoma cells in the blood. The cells were examined by flow cytometry for the presence of circulating epithelial cells. To determine whether the circulating epithelial cells were neoplastic cells, cytospin preparations were made after immunomagnetic enrichment and were analyzed. The malignant nature of the cells was demonstrated by their cytology and immunophenotype. The assay consists of using a series of mAbs that recognize the tissue-specific molecules. The first step involves an immunomagnetic sample preparation. After separation, sample volume is reduced and enriched for epithelial cells (which is essential for obtaining the sensitivity and low background required). Then the elements in the cell suspension are tagged using a second mAb specific for cytokeratin, a third mAb against a pan leukocyte antigen (CD45), and a nucleic acid dye. The sample is then analyzed by flow cytometry, and all events staining with the nucleic acid dye are analyzed for CD45 and cytokeratin staining and light scatter characteristics. To examine whether the cells identified as epithelial cells by flow

cytometry could be classified as tumor cells the cells were subjected to the immunomagnetic sample preparation followed by a cytospin that allows cells to be studied for morphology and additional markers. The total circulating epithelial cells measured by flow cytometry were used to assay for patients' clinical status over time. The goal of the assay was to perform screening entirely by immunomagnetic preparation followed by flow cytometry.

The antibodies CD45 and cytokeratin identify the cells as epithelial or non-epithelial based on the positive or negative staining of the cells viewed. This epithelial cell staining procedure was confirmed that the epithelial cells were tumor cells by studying the morphology and markers of individual cells by use of cytospin.

Claim 16 is not anticipated. The complex formed in Racila *et al.* was only used to indicate identification of epithelial cells, thus, the limitation "detection of the complex can distinguish a non-cancer cell from a cancer cell" is not met.

Claim 18 is also not anticipated. The limitation of claim 18, like the limitation of claim 16, is missing, as Racila's complex (immunostaining) only distinguishes between epithelial and non-epithelial, not non-cancer from cancer.

Further, claim 20 is not anticipated. As discussed above for claims 16 and 18, the limitation of claim 20, is missing, as Racila's complex (immunostaining) only distinguishes between epithelial and non-epithelial, not non-cancer from cancer.

This rejection should now be withdrawn.

Attached hereto is a marked-up version of the changes made to the specification and claims. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The examiner is invited and encouraged to

directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

The undersigned believes that a three-month extension of time is necessary to make this response timely. Payment in the amount of $1,004.00 ($920.00 for the extension of time and $84.00 for the addition of one independent claim) is to be charged to a credit card and such payment is authorized by the signed, enclosed document entitled: Credit Card Payment Form PTO-2038. This amount is believed to be correct. Should this be in error, Applicants respectfully requests that the Office grant such time extension pursuant to 37 C.F.R. § 1.136(a) as necessary to make this Reply timely, and hereby authorizes the Office to charge any necessary fee or surcharge with respect to said time extension or any additional fees which may be required, or credit any overpayment to the deposit account of the undersigned firm of attorneys, Deposit Account 14-0629.

Respectfully submitted,
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CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8

I hereby certify that this document and any documents referenced herein as being enclosed herein is being deposited with the United States Postal Service as first class mail in an envelope addressed to: BOX FEE AMENDMENT, Commissioner for Patents, Washington, D.C. 20231, on the date indicated below.

Patricia L. Ades — Date 09-23-2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

NOTE: ALL CLAIMS ARE INCLUDED FOR THE CONVENIENCE OF THE EXAMINER WHETHER THEY HAVE BEEN AMENDED OR NOT.

IN THE SPECIFICATION

No changes.

IN THE CLAIMS

1. (AMENDED) A method of screening for the presence of a cancer cell, comprising:
   a. obtaining a cell from a biological sample comprising a cell from a subject, wherein the sample is enriched for circulating epithelial cells by contacting the sample with an agent that binds with the epithelial cells;
   b. contacting the cell with a probe capable of hybridizing to a nucleic acid of the cell; and
   c. detecting the hybridization pattern of the probe, whereby the hybridization pattern can distinguish a non-cancer cell from a cancer cell, thereby screening for the presence of a cancer cell.

2. The method of claim 1, wherein the cell is a tumor cell.

[3. The method of claim 1, wherein the cell is an epithelial cell.]

[4. The method of claim 1, wherein the cell is a circulating cell.]

[5. The method of claim 4, wherein the circulating cell is a circulating epithelial cell.]

[6. The method of claim 5, wherein the cell is from a sample enriched for circulating epithelial cells.]

7. (AMENDED) The method of claim [6] 1, wherein the enrichment of the sample for circulating epithelial cells is achieved by cytokeratin screening.

8. The method of claim 1, wherein the probe is associated with a specific cancer, thereby identifying the organ-origin of the cancer cell.

9. The method of claim 1, wherein the probe is specific for a genetic marker.

10. The method of claim 1, wherein the probe is associated with a chromogenic dye.

11. The method of claim 1, wherein the probe is associated with a fluorescent dye.

12. The method of claim 1, wherein detection comprises spectral imaging.

13. The method of claim 1, wherein detection comprises utilizing multiple probes.

14. A method of screening for the presence of a cancer cell, comprising:
   a. obtaining a biological sample from a subject, wherein the biological sample comprises a mixed cell population suspected of containing a population of epithelial cells which include a cancer cell;
   b. mixing the biological sample with magnetic particles coupled to a ligand which is capable of reacting specifically with epithelial cells to the substantial exclusion of non-epithelial cells;
   c. enriching the biological sample for epithelial cells by subjecting the cells of step b to a magnetic field to produce a cell suspension that is enriched epithelial cells;

d. contacting the cells of step c with a probe capable of hybridizing to nucleic acid of the cell; and

e. detecting the hybridization pattern of the probe, whereby the hybridization pattern can distinguish a non-cancer cell from a cancer cell, thereby screening for the presence of a cancer cell.

15. (AMENDED) A method of determining the status of a cancer comprising:

a. obtaining a biological sample containing a cell from a patient diagnosed with cancer;

b. enriching the sample for circulating epithelial cells by contacting the sample with an agent that binds with the epithelial cells;

[b.] c. contacting the cell in the enriched sample with a probe capable of hybridizing to nucleic acid of the cell;

[c.] d. detecting the hybridization pattern of the probe, whereby the hybridization pattern can distinguish a non-cancer cell from a cancer cell;

[d.] e. determining the amount of cancer cells in the enriched sample and correlating the amount of cancer cells in the enriched sample with a stage of cancer, thereby determining the status of the cancer.

16. A method of determining the status of a cancer comprising:

a. obtaining a biological sample containing a cell from a patient diagnosed with cancer;

b. contacting the cell in the sample with a probe under conditions capable of forming a complex with an antigen of the cell;

c. detecting the complex, whereby detection of the complex can distinguish a non-cancer cell from a cancer cell;

d. determining the amount of cancer cells in the sample; and

e. correlating the amount of cancer cells in the sample with a stage of cancer, thereby determining the status of the cancer.

17. (AMENDED) A method of determining the progression of a cancer comprising:

a. obtaining a biological sample containing a cell at a first time point from a patient diagnosed with cancer and obtaining a biological sample containing a cell from the patient at a second time point;

b. enriching the first and second samples for circulating epithelial cells by contacting the samples with an agent that binds with the epithelial cells;

[b.] c. contacting the cell in the first enriched sample and the cell in the second enriched sample with a probe capable of hybridizing to nucleic acid of the cell;

[c.] d. detecting the hybridization pattern of the probe, whereby the hybridization pattern can distinguish a non-cancer cell from a cancer cell;

[d.] e. determining the amount of cancer cells in both the first enriched sample and the second enriched sample; and

[e.] f. comparing the amount of cancer cells in both the first enriched sample and the second enriched sample, whereby the relative amount of cancer cells in the first enriched sample as compared with the second enriched sample may be correlated with the progression of cancer, thereby determining the progression of the cancer.

18. A method of determining the progression of a cancer comprising:

a. obtaining a biological sample containing a cell at a first time point from a patient diagnosed with cancer and obtaining a biological sample containing a cell from the patient at a second time point;

b. contacting the cell in the first sample and the cell in the second sample with a probe under conditions which allow the probe to form a complex with an antigen of the cell;

c. detecting the complex in both the first sample and the second sample, whereby detection of the complex can distinguish a non-cancer cell from a cancer cell;

d. determining the amount of cancer cells in the first sample and the second sample; and

e. comparing the amount of cancer cells in both the first sample and the second sample, whereby the relative amount of cancer cells in the first sample as compared with the

second sample may be correlated with the progression of cancer, thereby determining the progression of the cancer.

19. (AMENDED)[20]. A method of determining the effectiveness of an anti-cancer treatment comprising:

a. obtaining a biological sample containing a cell from a patient that has been administered an anti-cancer treatment;

b. enriching the sample for circulating epithelial cells by contacting the sample with an agent that binds with the epithelial cells;

[b.] c. contacting the cell in the enriched sample with a probe capable of hybridizing to nucleic acid of the cell;

[c.] d. detecting the hybridization pattern of the probe, whereby the hybridization pattern can distinguish a non-cancer cell from a cancer cell;

[d.] e. determining the amount of cancer cells in the enriched sample and correlating the amount of cancer cells in the sample with the effectiveness of the anti-cancer treatment, thereby determining the determining the effectiveness of an anti-cancer treatment.

20.[21] A method of determining the effectiveness of an anti-cancer treatment comprising:

a. obtaining a biological sample containing a cell from a patient that has been administered an anti-cancer treatment;

b. contacting the cell in the sample with a probe under conditions capable of forming a complex with an antigen of the cell;

c. detecting the complex, whereby detecting the complex can distinguish a non-cancer cell from a cancer cell;

d. determining the amount of cancer cells in the sample and correlating the amount of cancer cells in the sample with the effectiveness of the anti-cancer treatment, thereby determining the determining the effectiveness of an anti-cancer treatment.

21. (NEW) A method for substantially simultaneously visualizing epithelial origin of a cell and the chromosome count of the cell comprising, in the following order:
    a. obtaining a biological sample containing a cell from a patient;
    b. performing immunocytochemistry on the sample to indicate epithelial origin;
    c. analyzing the stained cell for chromosomal count.

22. (NEW) The method of claim 21 wherein performing immunochemistry on the sample to indicate epithelial origin is treating the sample with a labeled antibody against cytokeratin.

23. (NEW) The method of claim 21 wherein analyzing the stained cell for chromosomal count is performing FISH analysis on the sample.

24. (NEW) The method of claim 1 wherein the biological sample is blood.

25. (NEW) The method of claim 1 whereby the hybridization pattern distinguishes a non-cancer cell from a cancer cell by detection of chromosomal aneuploidy specific for cancer.